COMPARISON OF EFFICACY OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACEIS) V/S ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS) IN MANAGEMENT OF MICRO ALBUMINURIA AMONG NORMOTENSIVE TYPE 2 DIABETIC PATIENTS

Muhammad Tahir, Wahaj Ul Hassan, Haji Muhamamd Aftab Alam

Combined Military Hospital Kohat, Pakistan

ABSTRACT

Objective: To compare the efficacy of Angiotension Converting Enzyme (ACEIs) v/s Angiotensin II Receptor Blockers (ARBs) in management of micro albuminuria among normotensive type 2 diabetic patients.

Study Design: Randomized controlled trial.

Place and Duration of Study: Department of Medicine, Combined Military Hospital, Kohat from Oct 2011 to Mar 2012.

Material and Methods: A total of 356 patients (178 in each group) between 30 and 60 years of age with newly diagnosed diabetes and having microalbuminuria fulfilling the inclusion criteria were selected through consecutive sampling and were enrolled in study. Patients were divided into two groups by random sampling. Group-1 (ACEIs) received enalapril 10mg/day while group-2 (ARBs) received losartan 50mg/day. Confounding variables were excluded using exclusion criteria.

Results: Mean age of the patients was 53.8 ± 8.7 and 53.1 ± 9.5 years in group-1 and group-2, respectively. Majority of patients in both groups were male. Efficacy was observed in 154 patients (86.5%) of group-1 and in 157 patients (88.2%) of group-2. Difference between two groups was non-significant (p>0.05).

Conclusion: ACEIs and ARBs both protect type 2 diabetic patients from developing protienuria.

Keywords: ACEIs, ARBs, Diabetes Type 2, Microalbuminuria.

INTRODUCTION

Diabetes mellitus type 2 is an important cause of mortality and morbidity, with nephropathy and retinopathy being the most prevalent complications. Around 40% of patients with diabetes have microalbuminuria [30 mg of albumin/gram of creatinine on a random urine sample (ratio > 0.03)].

Excretion of >30 mg/day of albumin in urine is the earliest manifestation of overt nephropathy[1]. Over 20 years, 40% of diabetics develop nephropathy and 20% even become dialysis dependent[2]. However if microalbuminuria is controlled along with good control of diabetes and blood pressure, normalization of renal structure can be achieved[3] and overt nephropathy can be prevented[4]. Guidelines of National Kidney Foundation and American diabetes association recommend treatment with either an Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotension II Receptor Blockers (ARB) as anti-hypertensive agents in diabetic nephropathy and chronic kidney disease[5]. Recent trials have favored use of ARBs over ACEIs for diabetic nephropathy[6]. A local study conducted in Lahore showed > 30% reduction in microalbuminuria with losartan in 87.1% type 2 diabetics[7]. However, an international study demonstrated that only ACEIs and not ARBs prevent and treat diabetic nephropathy[8].

Since accurate data about ACEIs' efficacy could not be found, a pilot study was conducted on 75 patients at Military Hospital (MH), Rawalpindi that showed 31% reduction in microalbuminuria in 77% type 2 diabetics with enalapril. Although ACEIs are mostly cheaper than ARBs, in Pakistan mostly ARBs

Correspondence: Dr Haji Muhammad Aftab Alam, House No 711, Mohallah Sardar Bahadar Khan Street Rehmat Ullah Tehsil & Disstt Khushab, Pakistan
Email: hmaftabalam@yahoo.com
Received: 24 Dec 2014; revised received: 28 Jan 2015; accepted: 26 Feb 2015

are prescribed to prevent microalbuminuria in type 2 diabetics based on international studies. Being a developing country with low resources, it is the dire necessity that studies be conducted to find the comparative efficacy of these drugs in prevention of microalbuminuria and diabetic nephropathy, so that an effective and affordable approach could be adopted.

The objective of this study was to compare the efficacy of ACEIs v/s ARBs in management of micro albuminuria among normotensive type 2 diabetic patients

MATERIAL AND METHODS

This study is randomized controlled trial, conducted at Department of Medicine, Combined Military Hospital (CMH) Kohat from October 2011 to March 2012. A total of 356 patients between 30 to 60 years of age with newly diagnosed diabetes and having microalbuminuria fulfilling the inclusion criteria were selected through consecutive sampling. Patients with hypertension, ischemic heart disease (IHD), Vasculitis, chromic kidney disease CKD (GFR < 60 ml/min), Nephrotic syndrome, glomerulonephritis, liver disease, Malignancy, UTI, and hyperkalemia (potassium > 4.6 mmol/l) were excluded from the study. Permission was obtained from "Hospital Ethical Committee". Written informed consent was obtained from the patients. Name, age, and hospital ID number were recorded. All selected patients were divided into two groups, with 178 patients in each group by random sampling. Venous blood sample was withdrawn and serum creatinine and serum potassium values were measured and recorded. Group-1 (ACEIs group) was prescribed enalapril 10 mg/day while group-2 (ARBs group) was prescribed losartan 50 mg/day. Microalbuminuria was calculated in urine spot sample by measuring Albumin Creatinine Ratio (ACR) at induction of study and after 6 months of drug therapy. Follow-up and compliance of all patients was ensured by taking telephone contact. Data was entered and analyzed in SPSS version 11. Chi square test was used to compare the efficacy in two groups.

Data analysis procedure

Data was entered and analyzed in SPSS version 11. Data comprised of quantitative variables i.e. age, ACR and qualitative variables i.e. gender, efficacy. Descriptive statistics, mean and standard deviation were calculated for quantitative variables like age of the patients, ACR. Frequencies and percentages were presented for qualitative variables like gender and efficacy. Results were presented with the help of tables. Chi square test was used to compare the efficacy in two groups. A *p* value less than 0.05 was considered significant.

RESULTS

Regarding age distribution, 37 patients (20.8%) in group-1 and 41 patients (23.1%) in group-2 were between 30-40 years old. A total of 56 patients (31.5%) in group-1 and 54 patients (30.3%) in group-2 were between 41-50 years old. The 51-60 year group was most common in both groups. Mean age of the patients was 53.8 ± 8.7 and 53.1 ± 9.5 years in group-1 and group-2, respectively (table-1). Majority of patients in both groups were males (table-2).

Table-1: Showing distribution of cases by efficacy.

Efficacy	Group-1 (ACEIs)		Group-2 (ARBs)	
	Number	%	Number	%
Yes	154	86.5	157	88.2
No	24	13.5	21	11.8
Total	178	100.0	178	100.

Chi square=0.10, df=1, *p* -value=0.749

Efficacy (defined as reduction of 30% or more from baseline microalbuminuria after 6 months use of ACEI or ARB) was observed in 154 patients (86.5%) of group-1 and in 157 patients (88.2%) of group-2. Difference between the two groups was non-significant ($p>0.05$) (table-3).

DISCUSSION

Diabetic nephropathy is the leading cause of end-stage renal disease. Use of ACE inhibitors is recommended by certain clinical guidelines in diabetic patients, both with

microalbuminuria and overt nephropathy, regardless of their blood pressure level[9]. Based on the results of four major renal outcome studies (Micro-HOPE, IRMA-2, RENAAL, IDNT studies), the American diabetes association has recommended ARBs for treatment of overt diabetic nephropathy, whereas patients with only microalbuminuria are recommended to be treated with either ACE inhibitors or ARBs[10,11]. To prevent the progression of nephropathy, about 55% to 75% of diabetic patients use ACEI or ARBs, as found in a large cohort[12].

With ACEI therapy, patients with mild renal insufficiency showed 53% reduction in the risk of becoming dialysis dependent. However those with moderate renal insufficiency showed 46% reduction in the same risk as shown in the ACE Inhibition in progressive renal insufficiency (AIPRI) study[13]. The Ramipril Efficacy in Nephropathy (REIN) study found that the use of ramipril in comparison with conventional antihypertensive drugs slowed the progression of fall in GFR and so progression to renal failure with same effects on blood pressure[14].

The results of the African American Study of Kidney Disease and Hypertension (AASK) also confirmed that ACEIs were associated with better renal outcomes than other antihypertensives in patients with hypertensive nephrosclerosis[15]. Unfortunately, the effects of ACEI versus ARBs on renal outcomes could not be shown with certainty in different studies owing to small sample sizes and short follow up times. Keeping in view these two factors, some investigators designed comparative trials of ACEI and ARBs. One example is the Diabetics Exposed to Telmisartan and EnalaprIL (DETAIL) trial, where effects of telmisartan and enalapril were found to be equal in reducing the decline in GFR. The serum creatinine values of all patients remained less than 200 µmol/L and none of the patient required dialysis during the five-year study period[16].

The effects of ACEIs in diabetic and non diabetic chronic kidney disease were analyzed by Kshirsagar. It was found that progression of renal failure in patients with chronic renal insufficiency was slower in patients treated with ACEIs, irrespective of blood pressure[17].

Another meta-analysis compared ACEI and ARBs with placebos and found greater benefits of both of these classes of drugs on all renal outcomes along with reduction in blood pressure that was not found with placebos. This finding lead to conclusion that the beneficial effect of ACEIs and ARBs was probably the result of blood pressure lowering properties of these drugs[18].

The actions of ACEIs in reducing the risk of end stage renal disease (ESRD) was challenged by Suissa et al. in their population based study. A total of 6,102 patients, both diabetic and non diabetic were prescribed antihypertensive drugs from 1982 to 1986 and were regularly followed till the end of 1997. By the end of the study, 102 patients had developed ESRD, out of which 21 were treated with ACEI during the intial three years[19].

In our study, both groups i.e ACEIs and ARBs were equally effective in management of microalbuminuria among normotensive type 2 diabetic patients (86.5% vs 88.2% respectively). A *p* value=0.749 was observed (non-significant). Our results are similar to the study of Matchar et al[20]. The differences between effects of ACE inhibitors and ARBs in diabetic patients with nephropathy could be explained by late referrals.

CONCLUSION

Both ACE-Inhibitors and ARBs preserve renal function and prevent progression from microalbuminuria to overt proteinuria in type 2 diabetics. Even in patients with already developed diabetic nephropathy, ARBs slow the progression to ESRD.

CONFLICT OF INTEREST

The authors of this study reported no conflict of interest.

REFERENCES

1. Saladin S, Balsamo C, Zucchini S, Miltonic G, Scorpion M, Rollo A, et al. High rate of regression from micro-macroalbuminuria to normoalbuminuria in children and adolescents with type 1 diabetes treated or not with enalapril: the influence of HDL cholesterol. Am Diabetes Assoc. Diabetes care. 2011 Feb;34(2):424-9

2. Lutale JJK, Thordarson H, Abbas ZG, Vetvik K. Microalbuminuria among Type 1 and Type 2 diabetic patients of African origin in Dar Es Salaam, Tanzania. BMC Nephrol. 2007;8:2
3. Molitch ME, Steffes M, Sun W. Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care. 2010;33:1536–43
4. Hall PM. Prevention of progression in diabetic nephropathy. Diabetes Spectrum. 2006;19:18-24.
5. National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive agents in chronic kidney disease. Guideline 8; Pharmacological therapy: Diabetic Kidney Disease. 2002.
6. Parvanova A, Chiurchiu C, Ruggenenti P, Remuzzi G. Inhibition of the renin-angiotensin system and cardio-renal protection: focus on losartan and angiotensin receptor blockade. Expert Opin Pharmacother. 2005;6:1931-42.
7. Agha A, Amer W, Anwar E, Bashir K. Reduction of microalbuminuria by using losartan in normotensive patients with type 2 diabetes mellitus: A randomized controlled trial. Saudi J Kidney Dis Transpl. 2009; 20:429-35.
8. Strippoli GF, Craig MC, Schena FP, Craig JC Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy and delay its progression. J Am Soc Nephrol. 2006;17:S153-5.
9. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis. 2002;39:S1–S246.
10. Molitch ME, DeFronzo RA, Franz MJ. Diabetic nephropathy. Diabetes Care. 2003;26:S94–S98.
11. Forclaz A, Maillard M, Nussberger J. Angiotensin II receptor blockade. Is there truly a benefit of adding an ACE Inhibitor? Hypertension. 2003;41: 31–6.
12. Rosen AB, Karter AJ, Liu JY, Selby JV, Schneider EC. Use of ACEIsand angiotensin receptor blockers in high-risk clinical and ethnic groups with diabetes. J Gen Intern Med 2004;19:669–75.
13. Maschio G, Alberti D, Janin G. Effect of the angiotensin- converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med. 1996;334:939-45.
14. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on longterm ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. Lancet. 1998;352:1252-6.
15. Agodoa LY, Appel L, Bakris GL. African American Study of Kidney Disease and Hypertension (AASK) Study Group. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA. 2001;285:2719-28.
16. Barnett AH, Bain SC, Bouter P. Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med. 2004;351:1952-61.
17. Andersen S, Rossing P, Juhl TR, Deinum J, Parving HH: Optimal dose of losartan for renoprotection in diabetic nephropathy. Nephrol Dial Transplant. 2002;17:413–8.
18. Casas JP, Chua W, Loukogeorgakis S. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet. 2005; 366:2026-33.
19. Suissa S, Hutchinson T, Brophy JM, Kezouh A. ACE inhibitor use and the long-term risk of renal failure in diabetes. Kidney Int. 2006;69:913-19.
20. Matchar DB, McCrory DC, Orlando LA. Systematic review: comparative effectiveness of ACEIsand angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med. 2008;148:16-29.

.....